- Measures have been taken, by the Utah Department of Health, Bureau of Health Promotions, to ensure no conflict of interest in this activity.
- CNE/CEU's are available for this live webinar. You must take the pre and post tests. 80% is required on the post test to receive CNE/CEU's.
- Certificates will be emailed out to you within two weeks

# Pregnancy & Diabetes: Strategies for Successful Outcomes

David Winmill, DNP, CDE, BC-ADM

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# David Winmill, DNP, ANP, CDE

- David Winmill, DNP, ANP, CDE is a graduate of Idaho State University with a Bachelor's of Science in Nursing and holds a Master's and Doctorate of Nursing Practice from the University of Utah College of Nursing. He has 17 years experience in Diabetes Management and Education and is currently in practice at the McKay Dee Endocrine & Diabetes Clinic.

# Successful Outcomes: Objectives

- Identify risks and complications associated with hyperglycemia in pregnancy
- Discuss role of preconception planning and appropriate goals for blood sugar control prior to and during pregnancy.
- Discuss and evaluate strategies for management of diabetes in pregnancy including use of oral medications and insulin therapy.
- Review and discuss appropriate diabetes care and management following delivery.

# Diabetes & Pregnancy: Statistics

- Gestational Diabetes affects up to 7 - 9% of registered births and accounts for 88% of all pregnancies affected by diabetes
- Pre-existing (Pre-gestational) diabetes identified in 1.3% of pregnancies
- In some studies, rates of diabetes affected pregnancy increasing for both GDM and pregestational diabetes (PGDM).
- Poor glycemic control carries significant risk for both mother and fetus.

DeSisto et al. (2014) *Prev Chronic Dis* 11:130415
Lawrence et al, (2008) *Diabetes Care.* 31(5)

# Pregestational Diabetes Mellitus

# Pre-gestational Diabetes Mellitus (PGDM)

- Defined as pre-existent Type 1 or Type 2 diabetes mellitus prior to conception.
- Increased risk for congenital malformations, materno-fetal complications, placental abnormalities & intrauterine malprogramming associated with hyperglycemia at conception and early pregnancy
- Risk for Macrosomia attributed to hyperglycemia occuring in the 2nd and 3rd trimester.

# Maternal Complications of Diabetes

**Spontaneous abortion**

**Hyperglycemia**

**Severe hypoglycemia**

**Diabetic ketoacidosis**

**Aggravation of end-organ disease (eye, heart & kidney)**

**Preeclampsia**

**Urinary tract infection**

**Chronic anemia**

**Cesarean delivery**

**Injury to genital tract**

**Postpartum hemorrhage**

**Post partum soft tissue infection**

Bernasko, (2004) *Obstet & Gynec Surv*, 59(8)
Leguizamón et al, *(2007) Obstet & Gynec Clin, 34(2*

# Fetal and Neonatal Complications of Diabetes

| Fetal | Neonatal |
| --- | --- |
| **Congenital anomalies** | **Respiratory distress syndrome** |
| **Fetal Demise** | **Hypoglycemia** |
| **Growth restriction** | **Hyperbilirubinemia** |
| **Polyhydramnios/Oligohydramnios** | **Serum electrolyte imbalance** |
| **Macrosomia** | **Death** |
| **Preterm Delivery** | |
| **Birth trauma** | |

Bernasko, (2004) *Obstet & Gynec Surv*, 59(8)
Leguizamón et al, (2007) *Obstet & Gynec Clin, 34(2)*

# Complications of Diabetes & Pregnancy

## Risk for congenital anomalies associated with hyperglycemia in first 7-8 weeks of pregnancy.

| System | Manifestations |
|---|---|
| Neurologic | Anencephaly, microcephaly, holoprosencephaly, neural tube defects |
| Cardiovascular | Transposition of great vessels, aortic coarctation with or without VSD or patent ductus arteriosus, atrial septal defect, single ventricle, hypoplastic left ventricle, pulmonic stenosis, pulmonary stenosis, pulmonary valve atresia, double outlet right ventricle truncus arteriosus |
| Gastrointestinal | Duodenal atresia, imperforate anus, anorectal atresia, small left colon syndrome, situs inversus |
| Genitourinary | Ureteral duplication, renal agenesis, hydronephrosis |
| Skeletal | Caudal regression syndrome (sacral agenesis), hemivertebrae |
| Other | Single umbilical artery |

Tyrala (1996) *Obstet & Gyn Clin 23(1)*

# Maternal Risk in Diabetes: Retinopathy

- Retinopathy may worsen during pregnancy; not as likely to present de novo
- Progression of retinopathy dependent on:
  - Level of existing retinal disease
  - Rapid reduction of hyperglycemia
- Milder forms of retinopathy typically regress after pregnancy, but more severe forms may persist or progress
- Gradual normalization of glucose levels recommended

Jovanovic and Nakai, (2006) *Endo Metab Clin 35 (1)*

# Maternal Risk in Diabetes: Cardiovascular Disease

- Type 1 diabetes (after 10 years) increases risk of MI from 1 in 10,000 in general population to 1 in 350.
- Odds ratio for pregnancy related MI for women with diabetes is 3.2 (1.5–6.9) $p<0.01$.
- Unrecognized and untreated coronary artery disease associated with (38%) maternal or fetal death, however no deaths reported with recognition and revascularization (CABG)

James et al, (2006) *Circulation,* 113(12*)*

# Maternal Risk in Diabetes: Nephropathy

- Microalbuminuria and nephropathy associated with increased risk preterm birth & preeclampsia
- Poorer fetal outcomes noted with kidney function impairment greater than 50%
- Reduced risk for progression of nephropathy with serum creatinine < 1.5 mg/dL and normal blood pressure.

Jovanovic & Nakai, (2006), *Endo Metab Clin 35 (1)*

# Gestational Diabetes Mellitus

# Gestational Diabetes Mellitus (GDM)

- Defined as any degree of glucose intolerance with onset or first recognition during pregnancy
- Increased risk for macrosomia, neonatal hypoglycemia, birth trauma, shoulder dystocia and jaundice
- Normalization of blood sugars occurs in most cases shortly after delivery
- Women with GDM significantly at risk to develop Type 2 Diabetes Mellitus (25.8% cumulative risk in 15 years).

# Gestational Diabetes Mellitus: Risk Factors

- Obesity
- Acanthosis nigricans
- Hypertension
- Previous GDM or delivery of an infant weighing more than 4000g
- Polycystic ovarian syndrome
- History of poor obstetric outcome
- Parent or sibling with T2DM
- High Risk Race/Ethnicity (Hispanic, Black, Native American)
- Mother's own birth weight >4000g

Blumer et al, (2013) *JCEM* 98(11)

# Diagnostic Criteria for Overt Diabetes & Gestational Diabetes at 1st Prenatal Visit for Women Not Known to Already Have Diabetes

| Diagnosis | Fasting Plasma Glucose | Untimed (Random) Plasma Glucose, | HgA1C % |
|---|---|---|---|
| Overt diabetes (type 1, Type 2, Other) | ≥ 126 mg/dL | ≥ 200 mg/dL | ≥ 6.5% |
| Gestational Diabetes | 92-125 mg/dL | N/A | N/A |

These criteria for the diagnosis of overt diabetes in early pregnancy are congruent with those of the American Diabetes Association

Testing should use plasma glucose analyzed at a laboratory, not capillary blood glucose analyzed with a blood glucose meter.

Performed using a method that is certified by the NGSP (National Glycohemoglobin Standardization Program) and standardized to the Diabetes Control and Complications Trial (DCCT) (39) reference assay.

Blumer et al, (2013) *JCEM* ; 98(11)
Castorino & Jovonavic. (2011) *Clin Chem* 57(2)

# Diagnostic Criteria for Overt Diabetes & Gestational Diabetes Using a 2 Hour 75-g OGTT at 24-28 Weeks Gestation

| Diagnosis | Fasting Plasma Glucose | 1 Hr Value | 2 Hr Value |
|---|---|---|---|
| Overt diabetes (type 1, type 2 or other) | ≥ 126 mg/dL | N/A | ≥ 200 mg/dL |
| Gestational Diabetes | ≥ 92mg/dL | ≥ 180 mg/dL | ≥153 mg/dL |

These criteria for diagnosing overt diabetes based on the results of the 24- to 28-week glucose tolerance test and consistent with recommendations of the American Diabetes Association and the IADPSG.

b Testing should use plasma glucose analyzed at a laboratory, not capillary blood glucose analyzed with a blood glucose meter.

ADA Standards of Medical Care (2015) 38(S77-S79)
Blumer et al, (2013) JCEM 98(11)

# Management of GDM

- Medical nutrition therapy and lifestyle changes can effectively manage 80% to 90% of mild GDM cases
- Medical nutritional therapy goals and recommendations:
  - Choose healthy low-carbohydrate, high-fiber sources of nutrition, with fresh vegetables as the preferred carbohydrate sources
  - Count carbohydrates and adjust intake based on fasting, premeal, and postprandial SMBG measurements[4,6]
  - Eat frequent small meals to reduce risk of postprandial hyperglycemia and preprandial starvation ketosis[5]
- As pregnancy progresses, glucose intolerance typically worsens; necessitating use of oral medications and ultimately insulin therapy

ADA Standards of Medical Care (2015) 38(S77-S79)

# Management Strategies to Improve Outcomes

# Diabetes Preconception Planning & Care

Care and management provided prior to pregnancy to reduce risk of fetal and maternal complications, consisting of the following components:

- Preconception Counseling
- Glycemic Control
- Management of Complications
- General Pre-pregnancy Care

# Serious Adverse Pregnancy Outcomes and A1C in Early Pregnancy

Prospective study of 1,215 pregnancies in 933 subjects with type 1 diabetes mellitus (58% Preconception Care).

| HgA1C >10.4% | Study | Gen Pop | RR | 95% C.I. |
|---|---|---|---|---|
| Congenital Anomaly | 10.9% | 2.8% | 7.3 | 1.8-7.8* |
| Perinatal Mortality | 5.5% | 0.75% | 3.9 | 2.5-19.8* |
| Adverse Outcome | 16.3% | 3.5% | 4.7 | 2.5-8.1* |
| HbA1C < 6.9% | | | | |
| Congenital Anomaly | 3.9% | 2.8% | 1.4 | 0.8-2.4 |
| Perinatal Mortality | 2.1% | 0.75% | 2.8 | 1.3-6.1* |
| Adverse Outcome | 5.6% | 3.5 | 1.6 | 1.0-2.6 |

*p<0.05

Jensen et al, (2009) *Diabetes Care 32(6)*

# Preconception Planning in Diabetes

- 50-60% of pregnancies are unplanned; often women are not aware they are pregnant until well-established
- Risk of congenital anomaly, perinatal mortality and adverse outcomes for women achieving A1C less than 6.9% approaches that of women without diabetes
- All women of child of child bearing age, with diabetes should be counseled of the need to avoid pregnancy and use reliable form of birth control until blood sugar well-controlled for 6 months
- Diabetes provider should be consulted regarding decision to become pregnant to advise and direct appropriate evaluation

# Diabetes Preconception Planning

- Establish glycemic control achieving a HgA1C less than 6.9% for 6 months. Ambulatory insulin pump therapy and CGMS may be considered.
- Dietary Consult to optimize nutrition and review integration of CHO with insulin dosing
- Review of medications and discontinuation of potentially teratogenic agents (ACEI, ARBs, statins)
- Screen for proteinuria and assess kidney function
- Ophthalmology consult
- Screening for Cardiovascular Disease

# Insulin Management for Diabetes in Pregnancy

- Glycemic control in the 1st trimester and throughout pregnancy associated with improved maternal, fetal and neonatal complications
- Insulin may be given by MDDI but delivery via Ambulatory Insulin Pump to be instituted during preconception
- Self Monitored Blood glucose measures fasting, before and after each meal and at bedtime.
- Women with Overt Type 2 diabetes controlled with oral agents often require insulin during pregnancy.

# Blood Glucose Monitoring

- Self monitoring of blood glucose (SMBG) a key component during pregnancy monitoring fasting, before and after meals and bedtime.
- Fingerstick SMBG recommended as alternate site testing may not detect rapid changes in glucose concentrations.
- Continuous glucose monitoring a useful supplemental tool for selected patients
- At times of illness or when blood sugars > 200 mg/dL, urine ketone measurements to detect ketonuria.
- HgA1C at initial visit then monthly until target levels < 6.0% and then every 2-3 months thereafter.

Kitzmiller et al. (2008) *Diabetes Care* 31(5)

# Glycemic Targets During Pregnancy

| Glucose Increment | Patients with GDM | Patients with Preexisting T1DM or T2DM |
|---|---|---|
| Preprandial, premeal | ≤95 mg/dL (5.3 mmol/L) | Premeal, bedtime, and overnight glucose: 60-99 mg/dL (3.4-5.5 mmol/L) |
| Postprandial, post-meal | 1-hour post-meal: ≤140 mg/dL (7.8 mmol/L) or 2-hour post-meal: ≤120 mg/dL (6.7 mmol/L) | Peak postprandial glucose 100-129 mg/dL (5.5-7.1 mmol/L) |
| A1C | A1C ≤6.0% | |

ADA Standards of Care. *Diabetes Care 2015* 38(S77-S79)
Blumer et al, *JCEM* 2013; 98(11)

# Insulin Therapy in Pregnancy

- NPH (Basal) & Regular insulin (Bolus) long considered the "approved" insulin therapy.
- Hypoglycemic risk due to onset, peak and duration profile
- Insulin aspart & lispro compared to Regular Insulin
  - Lower post-prandial blood sugar levels
  - Similar rates of neonatal hypoglycemia
  - Similar rates of perinatal mortality and congenital malformation
  - Both insulin aspart & lispro are designated Category B risk

Durnwald & Landon (2008) *J Mat Fetal Neonatal Med, 21(5)*
Hod et al. (2008) *Am J Obstet Gynecol, 198(2)*
Mathiesen et al. (2007) *Diabetes Care, 30(4)*

# + Insulin Choices in Pregnancy

| Insulin Options Considered Safe During Pregnancy | | | | | | |
|---|---|---|---|---|---|---|
| Name | FDA Risk | Type | Onset | Peak Effect | Duration | Recommended Dosing Interval |
| Aspart | B | Rapid-acting | 15 min | 30-90 min | 3-5 hours | Start of each meal |
| Lispro | B | Rapid-acting | 15 min | 30-90 min | 3-5 hours | Start of each meal |
| Regular insulin | B | Intermediate (basal) | 30-60 min | 2-4 hrs | 6 hours | 60-90 min before meal |
| NPH | B | Intermediate acting | 2 hr | 4-6 hrs | 8 hrs | Every 12 hrs |
| Detemir | B | Long-acting (basal) | 1 hr | n/a | 20-26 hrs | Every 12-24 hrs |
| Glargine | C | Long-acting (Basal) | 1 hr | n/a | 20-26 hrs | Every 12-24 hrs |

National Diabetes Information Clearinghouse 2013
http://diabetes.niddk.nih.gov/
Blumer et al, 2013

# Insulin Therapy & Pregnancy – Insulin glargine

- Insulin glargine the first long-acting (peak less) insulin analogue
- Pregnancy risk category C
- Research limited to retrospective studies with similar outcomes compared to NPH insulin
  - Maternal HgbA1C
  - Birth weight
  - Neonatal complications/congenital malformations/macrosomia
  - Neonatal hypoglycemia

Egerman et al (2009) *Am J Perinatol, 26(8)*
Fang et al (2009) *J Matern Fetal Neonatal Med, 22(3)*
Henderson et al (2009) *J Reprod Med, 54(4)*
Smith et al (2009). *Am J Perinatol, 26(1)*

# Insulin Therapy & Pregnancy – Insulin detemir

- Insulin detemir the second long-acting insulin analogue
- Pregnancy risk category B (2012)
- Recent open-label, controlled, randomized trial in 310 pregnant subjects with type 1 diabetes receiving insulin detemir vs. NPH (and mealtime Novolog).
  - HgA1c 6.27% (insulin detemir) and 6.33% (NPH)
  - More severe hypoglycemia in NPH subjects (20.9%) vs. insulin detemir (16%).
  - Incidence for non-severe episodes similar between groups.
  - No significant differences in pregnancy outcomes

*)*

Hod et al. (2014) *J Matern Fetal Neonatal Med, 27(1, )*

# Glyburide & Pregnancy

- Classification: Oral hypoglycemic sulfonylurea
- Pregnancy risk: Category B
- Mechanism of action: Stimulation of insulin via pancreatic beta cells.
- Pivotal randomized trial of 404 women comparing glyburide vs. insulin found no difference in complications.
  - Percent LGA (12% glyburide vs. 13% insulin; (P = 0.76)
  - Macrosomia (7% glyburide vs. 4% insulin; (P = 0.26)
  - Pulmonary complication (9% glyburide vs. 6% insulin: (P = 0.43 )
  - Neonate Requiring NICU (6% glyburide vs. 7% insulin; (P = 0.74)

Langer et al (2000) *N Engl J Med, 343(16)*

# Metformin & Pregnancy

- Biguanide class of oral hypoglycemic
- Pregnancy risk:  Category B – no teratogenicity in animal models up to 6 times  maximum recommended human dose.
- Reduces hepatic glucose production
  - Decreased gluconeogenesis/glycogenolysis
  - Enhanced insulin-mediated glucose uptake
  - Does not stimulate insulin production (hypoglycemia rare)
- Other Effects
  - Improved fertility
  - Reduces rate of recurrent miscarriage
  - No reports of increased birth anomalies.

Langer et al. (2007)  Obstet Gynecol Clin North Am  34 (2)
Gilbert et  al (2006). Fertil Steril  36:3

# Dietary Recommendations

- All women with diabetes should receive individualized medical nutrition therapy (MNT) based on individual preferences to include
  - Appropriate calorie level
  - Adequate consumption of protein, fats and micronutrients.
  - Assess pregravid BMI and target individual gestational weight gain at lower range of Institute of Medicine recommendations.
  - Consumption of 175 g/day digestible carbohydrate, distributed to promote optimal glycemic control and avoid hypoglycemia, hyperglycemia and ketonemia.
- Recommend folate at 600 μgm/day during periconception and prenatal periods.

Kitzmiller et al.(2008) *Diabetes Care* 31(5)

# Diabetes & Post-partum Care

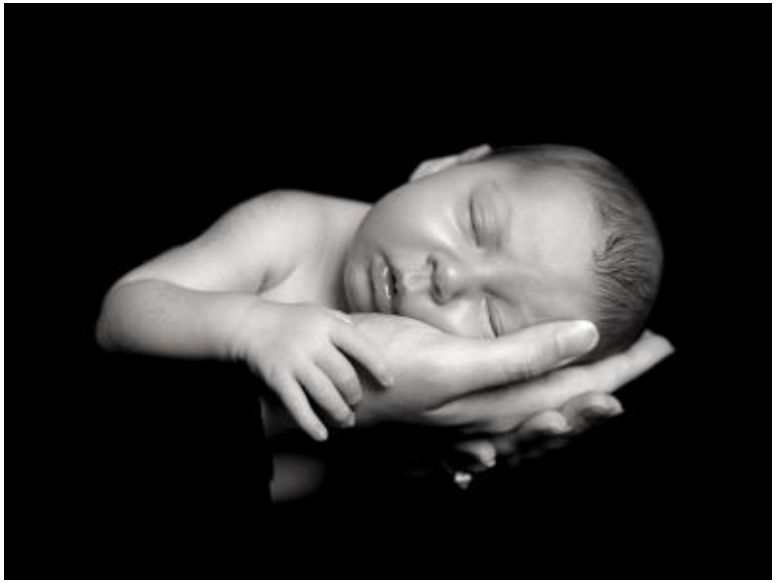
- For most women with PGDM, insulin requirements return to pre-pregnancy levels shortly after delivery.

- Recommendations for women with GDM:
  - Continue monitoring  blood glucose levels for 24-72 hours after delivery
  - Glucose lowering medication can be discontinued unless overt diabetes suspected.
  - Lifestyle measures to reduce risk of type 2 diabetes mellitus
  - Should undergo 2 hour, 75g OGTT at 6-12 weeks post-delivery and repeated periodically and before future pregnancies.

# Summary

- Greatest risk for fetal anomaly exists with hyperglycemia in the first 7-8 weeks gestation.
- Greatest risk for macrosomia and related birth trauma, exists with hyperglycemia in the 2nd & 3rd trimesters.
- Preconception planning is an integral element of care for diabetes management of pregnancy
- With appropriate screening, diagnosis and management of diabetes in pregnancy outcomes can be improved to nearly that of women with out diabetes
- A multi-disciplinary approach, including the diabetes provider, diabetes educators and dietitian are key to success and good outcomes for pregnancy in women with diabetes

# Thank You!



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